REMARKS

Formal Matters

Applicants thank the Examiner for kindly discussing this application and making very helpful suggestions regarding amendments to the claims that would overcome the pending rejections. Applicants have amended claims 1, 6, 13, 16, and 33 accordingly. No new matter has been added to the claims by way of these amendments. Applicants also canceled claims 7-8, 17-18, and 22-32.

Claims 1, 4, 6, 9-16, 19-21, and 33 are now pending in this application.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 4, and 6-33 have been rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner specifically rejected claims 1, 13, and 22 because it is "unclear if the requirement of the claim is that the patient be actually exhibiting impaired consciousness at the time of treatment." Office Action at page 2. Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants have removed the phrase "associated with impaired consciousness" and have further revised the preamble at the suggestion of the Examiner to recite "A method for treating hypercalcemic crisis associated with malignant tumor." In light of this amendment, Applicant respectfully requests that the Examiner withdraw this rejection.

The Examiner rejected claim 1, because allegedly "[i]t is unclear how 'a blood calcium level' relates to the method preamble of treating a patient." Office Action at page 2. Further, it is allegedly unclear "how the method step of 'decreasing a blood calcium level' and 'maintaining the at least 1 mg/dl decrease' is related to the administration of the humanized anti-PTH-rP antibody." Id. Applicant respectfully submits that the method of claim 1 is clear to one of ordinary skill in the art when read in light of the Specification. The Specification states that "[p]articularly in patients with hypercalcemic crisis, since the rapid increase in blood calcium level may sometimes lead to death, it is needed to decrease the blood calcium level as soon as possible." Specification, at page 3, lines 20-23. Thus, as a means of treating hypercalcemic crisis patients, it is desirable that their blood calcium level be decreased. Further, other drugs that are used to treat hypercalcemia lose their therapeutic effect when successively administered (see Specification at page 3, lines 15-19), thus it is also desirable that any decrease in calcium level be maintained over an extended period of time. Applicant has demonstrated the ability of an anti-PTHrP antibody to decrease, and maintain said decrease, in an animal model of hypercalcemic crisis. See Specification, Example 1, pages 24-28. Nevertheless, and at the suggestion of the Examiner, Applicants have amended the claim to recite that "said blood calcium level decreases to below 15 mg/dl." In light of this evidence and the claim amendment, Applicant respectfully requests the Examiner withdraw this rejection.

The Examiner rejected claim 4, stating that "[i]t is unclear how claim 4 further limits claim 1 as the property of inhibiting the binding between PTH-rP and a receptor

thereof recited in claim 4, is a limitation of the antibody recited in claim 1." Office Action at page 2. Applicants respectfully submit that claim 4 limits claim 1 to an antibody fragment. Applicants also submit that "fragment" is a term that is understood by someone of ordinary skill in the art. Further, examples of antibody fragments are given in the Specification at, for instance, the paragraph spanning pages 15 and 16. In light of this evidence, Applicant respectfully requests the Examiner withdraw this rejection.

The Examiner noted that claim 33 recites "the method according to claim 2." As claim 2 is canceled, Applicant amended claim 33 to recite "the method according to claim 1."

The Examiner rejected claims 7, 17, and 28 for allegedly being unclear as to how they limit the scope of independent claims 1, 13, 14, 22, or 25. Further, the Examiner stated that "it would be inherent that the humanized antibodies of claims 1, 13, 14, 22, or 25 were also monoclonal antibodies." Office Action at page 3. Applicants respectfully traverse. However, merely to expedite prosecution, Applicants canceled claims 7, 17, and 28, thereby rendering the Examiner's rejection moot.

Claims 6, 16, and 27, are rejected as being "vague and indefinite in the recitation of #23-57-137-1 as the only means of identifying the monoclonal antibody on which the claims depend." Office Action at page 3. Applicants respectfully traverse. The hybridoma clone #23-57-137-1 is clearly described in the Specification along with deposit information under the terms of the Budapest Treaty. *See, e.g.*, Specification at page 8, lines 17-21; Specification at page 29, lines 14-18. The Examiner stated that "[a]mendment of the claims to recite the Deposit Accession Number would overcome

this rejection." Office Action at page 3. Therefore, merely to expedite prosecution, Applicants have amended claims 6 and 16 to recite the Deposit Accession Number. Applicants have cancelled claim 27. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Obviousness and Double Patenting Rejections

In the Office Action, the Examiner makes several obviousness rejections.

- Claims 22-26 and 28-31 are rejected as being obvious over *Seger* (U.S. Patent No. 5,494,806) in view of *Potts* (Diseases of the Parathyroid Gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's Principles of Internal Medicine, 12th Edition, pages 1902-1915) and *Schlom* (In: Molecular Foundations of Oncology, Sameule Broader, Ed., 1991, pages 95-134). Office Action at page 6.
- Claims 22-26 and 28-32 are also rejected as being obvious over *Seger* and *Potts* and *Schlom* and further in view of *Gristina* (U.S. Patent No. 5,681,565). Office Action at page 9.
- Claims 22-23, 27-30 are rejected as being obvious over the abstract of *Sato* (WO 98/13388) in view of *Potts.* Office Action at page 10.
- Claims 22-30 are also rejected as being obvious over *Sato* and *Potts* and further in view of *Schlom.* Office Action at page 12.
- Claims 22-30 are rejected as being obvious over *Sato* and *Potts* and *Schlom* and further in view of *Gristina.* Office Action at pages 12-13.
- Claims 22-30 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 126-136 and 138 of copending Application No. 09/269,332, in view of *Potts* and *Schlom.* Office Action at page 13.
- Claims 22-32 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 126-136 and 138 of copending Application No. 09/269,332 in view of *Potts* and *Schlom* in further view of *Gristina*.

Applicants respectfully disagree with these rejections, but have cancelled claims 22-32 to facilitate prosecution of the remaining claims in this application. Applicants reserve the right to prosecute these claims at a later date.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 13-32 have been rejected by the Examiner under 35 U.S.C. § 112 as allegedly "failing to comply with the written description requirement." Office Action at page 3. Specifically, the Examiner alleges that "neither the specification nor claims as filed provide support for the specific limitation of 15 mg/dl." Exhibit 2, provided in the Office Action Response of September 20, 2002, cited in the Specification at page 2, lines 5-6 and incorporated in its entirety on page 79, lines 1-2 describes that when the blood calcium level becomes 3.7-4.5 mmol/l (15-18 mg/dl) or greater, there is concern about coma or cardiac arrest occurring. Harrison's Text for Internal Medicine, page 3427, Internal Medicine, 1081-1084, Asakura Shoten, left column, lines 9-11.

Because this reference is incorporated in its entirety on page 79, lines 1-2 of the Specification, it is possible to amend the Specification to include the material incorporated by reference. This amendment is accompanied by an attorney affidavit, stating that the amendatory material consists of the same material incorporated by reference in the referencing application and thus no new matter has been added. *See* MPEP § 608.01(p)(2). Applicants have made the amendment and request that the Examiner amend the Specification and withdrawn the rejection.

The Examiner also alleges that the values described in the Specification at page 6, lines 6-22 "do not provide support for the broader claim [22] drawn to 'decreasing a blood calcium level to effectively treat the patient'." Office Action at page 3. Further, "the specification makes no mention of using the instant methods as 'fall back' in the case that the hypercalcemia is resistant to calcitonin, furosemide, etc." Office Action at

page 4. Applicants have cancelled this claim without prejudice and request that this rejection be withdrawn.

Enablement Rejections

The Examiner rejected claims 1, 4, 6-21 and 33, as failing to comply with the enablement requirement. Office Action page 4. In regards to claim 1, the Examiner states that "[a] reduction of only 1 mg/dl or 2 mg/dl at the minimum danger level of 15 mg/dl will not reduce the calcium level in the blood of said patient to the point at which the patient is out of danger from cardiac arrest and coma." *Id.* In regards to claim 13, the Examiner states that "decreasing the blood calcium level to 15 mg/dl does not decrease the calcium level to the point at which the patient is out of danger for cardiac arrest and coma." Office Action at page 5.

During the interview, Applicants and the Examiner discussed the claim amendment "below 15 mg/dl" and Applicants have made that amendment in this response. Typical treatments for hypercalcemia, such as calcitonin and biphosphonate, are unable to decrease and then maintain the decrease in the calcium level in a hypercalcemic crisis patient. A reduction to a blood calcium level of below 15 mg/dl reduces the susceptibility of the patient to the severe symptoms associated with hypercalcemic crisis, such as impaired consciousness. Blood calcium levels below 15.0 mg/dl would not be in the hypercalcemic crisis range (15-18 mg/dl), as it is now defined in the Specification. Applicants, thus, request that this rejection be withdrawn.

The Examiner also rejected claims 1, 4, and 6-33 because the Specification "does not reasonably provide enablement for methods of treating hypercalcemic crises having increased calcium levels from other causes than elevated levels of PTHrP." Office Action at page 5. Further, the Examiner cites Sato (Journal of Bone and Mineral Research, 1993, vol. 8, pp. 849-860), which allegedly demonstrates that "immunization of a hypercalcemic mouse bearing a transplanted parathyroid carcinoma which secretes PTH rather than PTH-rP, did not effect the blood calcium concentration." *Id.* at 6. Applicants have amended the preamble of claim 1 and 15 to read "A method for treating a patient suffering from or susceptible to hypercalcemic crisis associated with malignant tumor." Applicants have also cancelled claims 8 and 18, which do not further limit the claims as amended. Applicants request that the Examiner withdraw this rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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